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Decoding the HPV-Positive HNSCC Paradox: Suppression of Oncogenic Drivers and Inflammatory Signalling Creates a Distinct Tumor Microenvironment

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Abstract: Head and neck squamous cell carcinoma (HNSCC) is a significant global health concern. Though tobacco, alcohol, and betel quid have been previously recognized as the main risk factors for a long time, unique cases of human papillomavirus (HPV) infection-mediated cancer are now a very emerging topic of discussion. HPV-mediated tumors show distinct biological and clinical properties. Interestingly, it has been observed that though HPV-positive HNSCC often is the sole cause for advanced-stage cancers, patients still have far better initial survival outcomes than those with HPV-negative disease. To better understand this paradox, we carried out integrated transcriptomic and epigenomic analyses using TCGA and other publicly available datasets. Our results depict that HPV-positive tumors suppress some key oncogenic drivers, such as MMP1, MMP11, PTHLH, and SPRR2G, along with some very important pro-inflammatory cytokines like IL1α, IL1β, and TNF. Whereas, all of these genes have many-fold higher expression in the HPV-negative scenario. This change in gene expression profile weakens pathways involved in invasion, extracellular matrix remodeling, and chronic inflammation, ultimately creating a less aggressive tumor environment in HPV-positive HNSCC. On a mechanistic level, we observed HPV-positive cells modulating havoc in chromatin regulation. Specifically, they lose H3K27ac and replace RELA binding with p63 at various pro-inflammatory cytokine promoters, shifting the transcriptional control toward epithelial survival pathways. This duality—reduced inflammatory signalling along with reinforced epithelial persistence—helps to understand why HPV-positive tumors are associated with a more favorable prognosis. In summary, our study establishes HPV-positive HNSCC as biologically different cancer types shaped by viral regulation of chromatin, transcription factors, and immune signalling, offering altogether a new insight into the unique clinical outcomes.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the major global health concerns, becoming the leading cause of cancer-related illness and death (Barsouk et al., 2023). Every year, more than 650,000 new cases of cancer are diagnosed, and among them, nearly 330,000 patients lose their lives fighting this age-old disease (Barsouk et al., 2023). Tobacco use, alcohol consumption, and betel quid chewing have traditionally been detected by various researchers as the main risk factors—particularly in developing regions of the world (Zeng et al., 2019). Recent evidence has shown certain different peculiarities that do not at all follow this pattern of HNSCC development. Our research highlights one such peculiarity of HNSCC driven by human papillomavirus (HPV) (Qin et al., 2021), establishing viral infection as a significant and

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previously underappreciated player in the tumor development. Through our comprehensive analyses, we observed that patients with HPV-positive HNSCC experience distinctly different clinical outcomes compared to HPV-negative patients. Even though both groups of cancer show an advanced level of the disease, initially HPV-positive patients tend to respond better to treatment and show improved survival rates (Psyrri & Cohen, 2011). Even HPV-positive tumor shows relatively slower growth at the advanced level of the disease. Our work suggests that this surprising difference arises because HPV fundamentally changes host transcriptional programs and immune responses. Specifically, HPV suppresses pro-inflammatory cytokine signalling, remodels the enhancer area, and helps to recruit alternative transcription factors that may lead to a very unique tumor microenvironment (Castellano et al., 2022). While the viral oncoproteins E6 and E7 are well known for disrupting p53 and Rb, our findings reveal that HPV's effects extend well beyond these classic pathways (Vats et al., 2021), and it can also interact with other proteins for tumor development. We demonstrate that HPV-positive tumors show reduced expression of HNSCC-specific common oncogenic genes, widespread suppression of different pro-inflammatory cytokines, and chromatin remodelling that shifts promoter activity. This reprogramming not only dampens immune signalling but also reinforces a tumor environment that supports cancer growth while maintaining reduced aggressiveness. In summary, our study positions HPV as a critical driver of HNSCC pathogenesis with unique biological consequences. By detecting how HPV starts reshaping both molecular and immune landscapes, we provide new insights into why HPV-positive tumors consistently have more favorable histological and clinical outcomes. These findings underscore the importance of developing HPV-specific biomarkers so that a HPV-positive growth does not evade the detection because of its slow growth and therapeutic strategies, as traditional inflammation-based markers may not be sufficient for early detection or patient stratification in this HPV-positive HNSCC subgroup.

Materials and Methods

Data Acquisition

Transcriptomic data were obtained from the TCGA database through the University of ALabama at Birmingham CANcer data analysis, UALCAN portal (Chandrashekar et al., 2017). The TCGA-HNSCC tumor cohort has 520 cancer samples and 44 normal controls. The HNSCC tumor group has been analysed for different oncogenic genes and cytokine profiles. These analyses were further compared with HPV status using metadata available in the TCGA-UALCAN resource. Various clinical information—such as tumor stage, disease-specific survival, and progression-free survival—was collected from the TCGA UCSC-XENA platform (Goldman et al., 2020).

Differential Expression Analysis

Differential gene expression between HPV-positive and HPV-negative tumors was assessed using DESeq2 (Love et al., 2014) tool on the publicly accessible dataset GSE65858 (Guo et al., 2023). Genes were selected for the analysis with a characters of false discovery rate (FDR) below 0.05 and an absolute log2 fold change greater than 1. The extracted genes from the dataset have been used to make a volcano plot. The plot was created with SR Plot tool (Tang et al., 2023). Expression patterns in cell lines were also analyzed through the DepMap database (Shimada et al., 2021), and results were visualized using the ClustVis heatmap tool (Metsalu & Vilo, 2015).

Pathway Analysis

The 200 most significant differentially expressed genes were evaluated for pathway enrichment using the clusterProfiler package (Yu et al., 2012) of DAVID functional annotation tool (Huang et al., 2007). KEGG and Reactome databases were used as references, with a focus on pathways related to immune responses (Kanehisa & Goto, 2000; Croft et al., 2011).

Epigenomic Integration

Publicly available ChIP-seq data from ChIP-Atlas (Zou et al., 2022) were used to assess histone modification (H3K27ac, H3K4me3) and transcription factor occupancy, (including p63, RELA), at loci of inflammatory cytokine genes. SRX3244984 (Ref. - GSE65858) dataset has been

employed for the ChIP-seq analysis (Jin et al., 2024). All the analysis here has been done against hg38 of human genome database.

Statistical Analysis

Survival analyses were performed using the R survival package of UCSC-XENA. Kaplan–Meier plots were generated (Goel et al., 2010). Log-rank tests were applied to evaluate differences between groups. Unpaired t-tests (Kim, 2015) were used to compare distributions of tumor stage across HPV-positive and HPV-negative cases.

Results

HPV-positive HNSCC exhibits suppressed oncogenic gene expression and improved survival outcomes compared to HPV-negative disease

To better understand how gene expression differs between HPV-positive and HPV-negative tumors, we analyzed the most significantly altered genes in HNSCC. Figure 1A highlights the top five overexpressed genes in HNSCC compared with normal tissues, whereas Figure 1B shows the five most downregulated genes in HNSCC. These two groups represent potential oncogenic genes and tumor suppressors that are consistently disrupted in HNSCC. Interestingly, some of the genes that are usually highly overexpressed in HNSCC (Figure 1A) showed a marked reduction in expression in HPV-positive tumors (Figure 1C–D) when we analysed those genes against the HPV-negative counterparts. In other words, while these genes remain strongly upregulated in HPV-negative cancers, HPV infection appears to suppress their expression. This creates a paradoxical event where HPV-positive tumors display a “less malignant” transcriptomic profile than their negative counterparts, but HPV is already a known carcinogenic agent. Survival analysis further revealed that patients with HPV-positive disease showed a better clinical outcome compared with those who were HPV-negative (Figure 1E). This clearly shows that HPV-positive HNSCC is associated with a more favorable prognosis. Taken together, these findings suggest that HPV-positive tumors display a “pseudo-suppressed” molecular signature, with classical oncogenic drivers or genes being dampened in expression.

HPV-positive HNSCC tumors and cell lines show suppressed pro-inflammatory cytokine signaling despite similar rates of advanced-stage disease

Figure 2A shows the percentage of advanced-stage disease (stage III–IV) in HPV-positive and HPV-negative HNSCC patients. Both distributions are largely comparable, meaning HPV-positive tumors are also progressive towards the cancer stage advancement. However, as the previous figure suggested, their clinical course appears slower and biologically distinct from HPV-negative HNSCC. Figure 2B highlights a clear trend in cytokine expression. Major Pro-inflammatory cytokines such as IL1α, IL1β, and TNF are significantly reduced in HPV-positive tumors, while some anti-inflammatory cytokines (such as IL10, IL13 and IL4) show increased expression. This suggests HPV infection reshapes the cytokine landscape into a less inflammatory state, which could influence how the tumor interacts with the immune system. We also have analysed the publicly available RNA-Seq data (Ref.- GSE65858) from HNSCC HPV-Pos and HPV-Neg cell lines to reconfirm our clinical data. Our analysis of RNA-Seq in Figure 2C shows HPV-positive lines exhibit strong suppression of pro-inflammatory cytokine expression, matching the patient tumor data. Anti-inflammatory cytokines, however, display more variability across cell lines, possibly due to cell-specific differences or compensatory signalling. Figure 2E further validates this in different HPV-positive and HPV-negative cell lines, which showed reduced expression of pro-inflammatory cytokines at the transcriptional level. These analyses prove pro-inflammatory cytokines have been majorly targeted by HPV infection. The reproducibility across different systems strengthens the evidence that HPV actively suppresses inflammatory signaling. To dig deeper, pathway analysis (DAVID/KEGG) was performed on the top 200 upregulated and downregulated genes (Fig. 2D).

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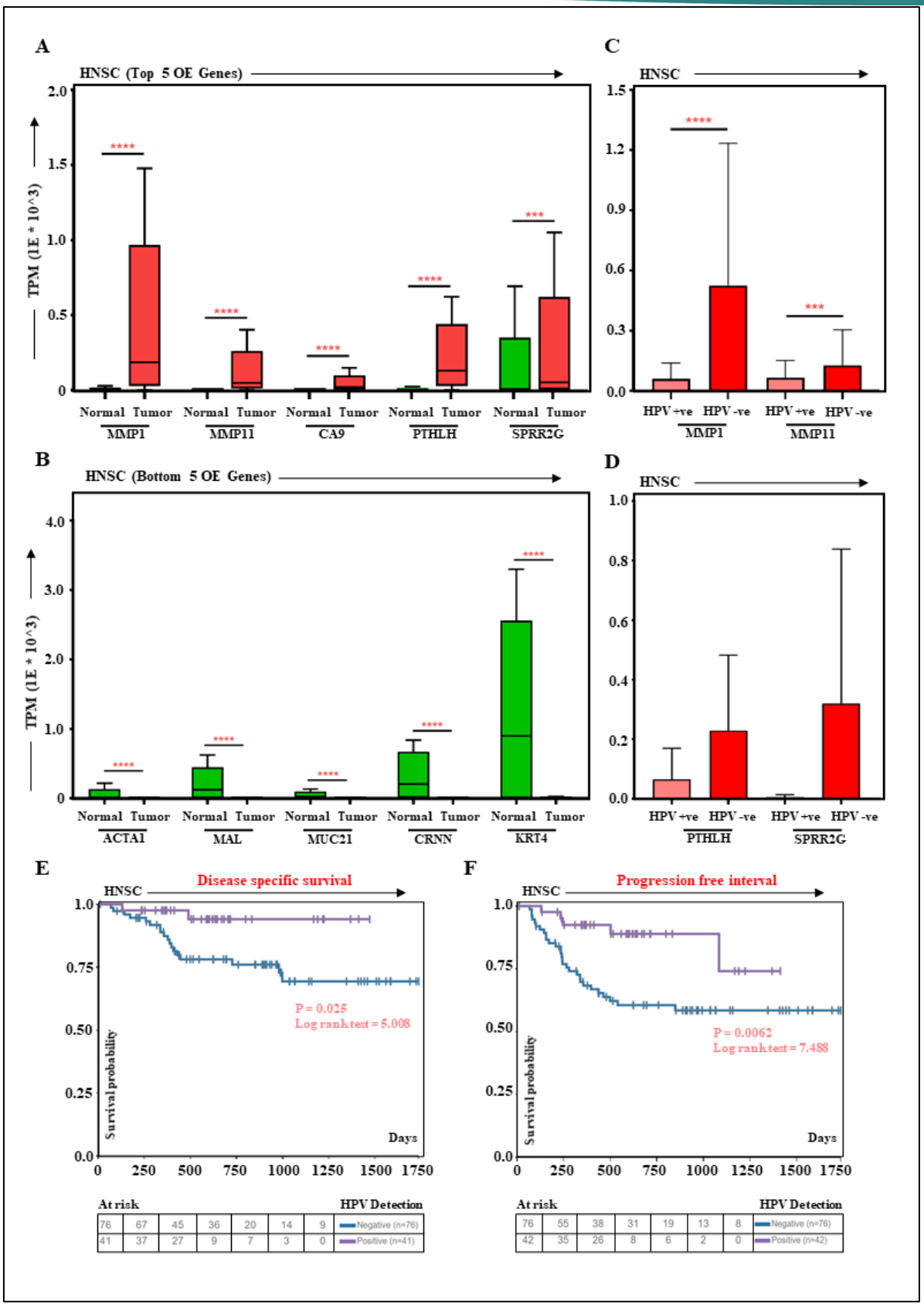

Figure 1. Figure 1. HPV-positive HNSCC shows reduced activation of key oncogenic drivers and is linked to improved patient survival compared to HPV-negative tumors. (A) The top five genes found to be highly overexpressed in HNSCC when compared with normal tissue. (B) Bottom five genes most strongly downregulated in HNSCC relative to normal samples. (C–D) Comparative analysis of these genes between HPV-positive and HPV-negative tumors illustrates that several oncogenic drivers are less active in HPV-positive cases. (E) Kaplan–Meier survival curves demonstrating overall survival differences, with HPV-positive patients exhibiting a significantly more favorable prognosis than HPV-negative patients.

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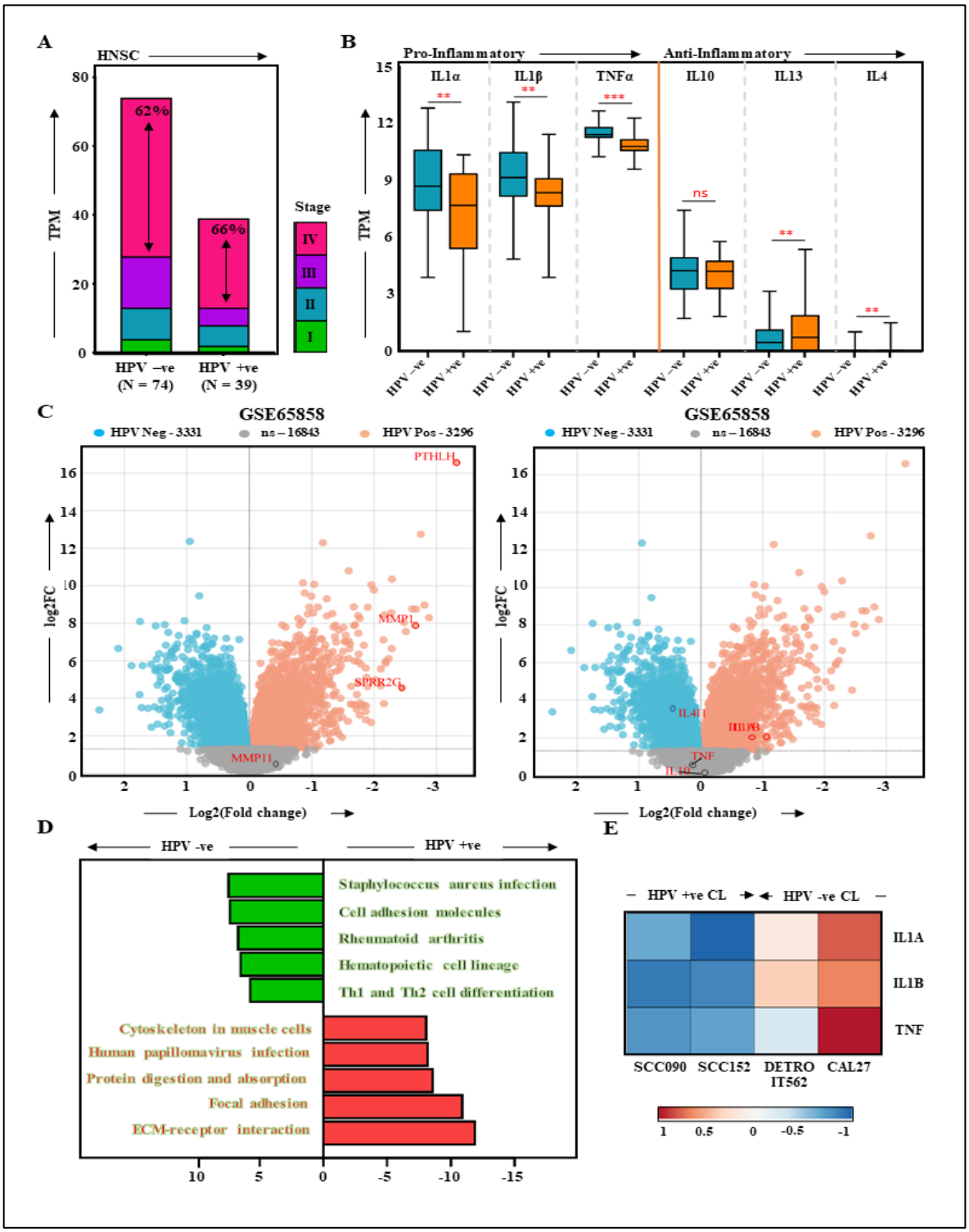

Figure 2. HPV-positive HNSCC tumors and cell lines show reduced pro-inflammatory cytokine activity despite having similar rates of advanced-stage disease. (A) The distribution of advanced-stage cases (stage III–IV) is comparable between HPV-positive and HPV-negative HNSCC patients. (B) Cytokine expression analysis reveals a marked decrease in pro-inflammatory cytokines (IL1α, IL1β, TNF) in HPV-positive tumors, along with a relative increase in certain anti-inflammatory cytokines. (C) RNA-seq profiling of HPV-positive versus HPV-negative HNSCC cell lines shows a consistent reduction in pro-inflammatory cytokine expression in HPV-positive cells, though anti-inflammatory gene expression varies. (D) KEGG pathway enrichment of the top 200 differentially expressed genes demonstrates broad suppression of inflammation-related pathways in HPV-positive tumors. (E) Analysis of independent cell line datasets further validates the significant downregulation of pro-inflammatory cytokine expression in HPV-positive models. CL = Cell Line.

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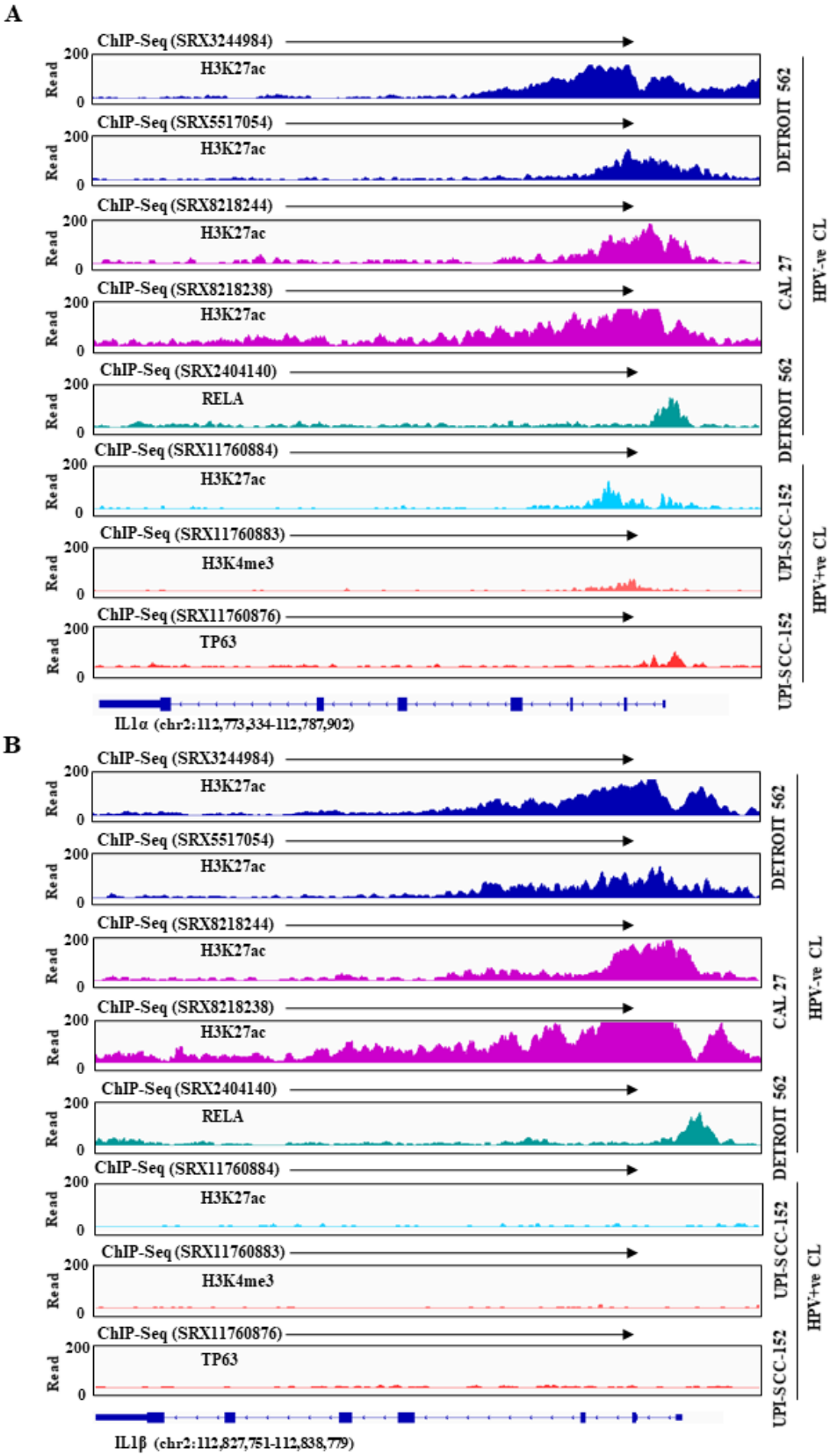

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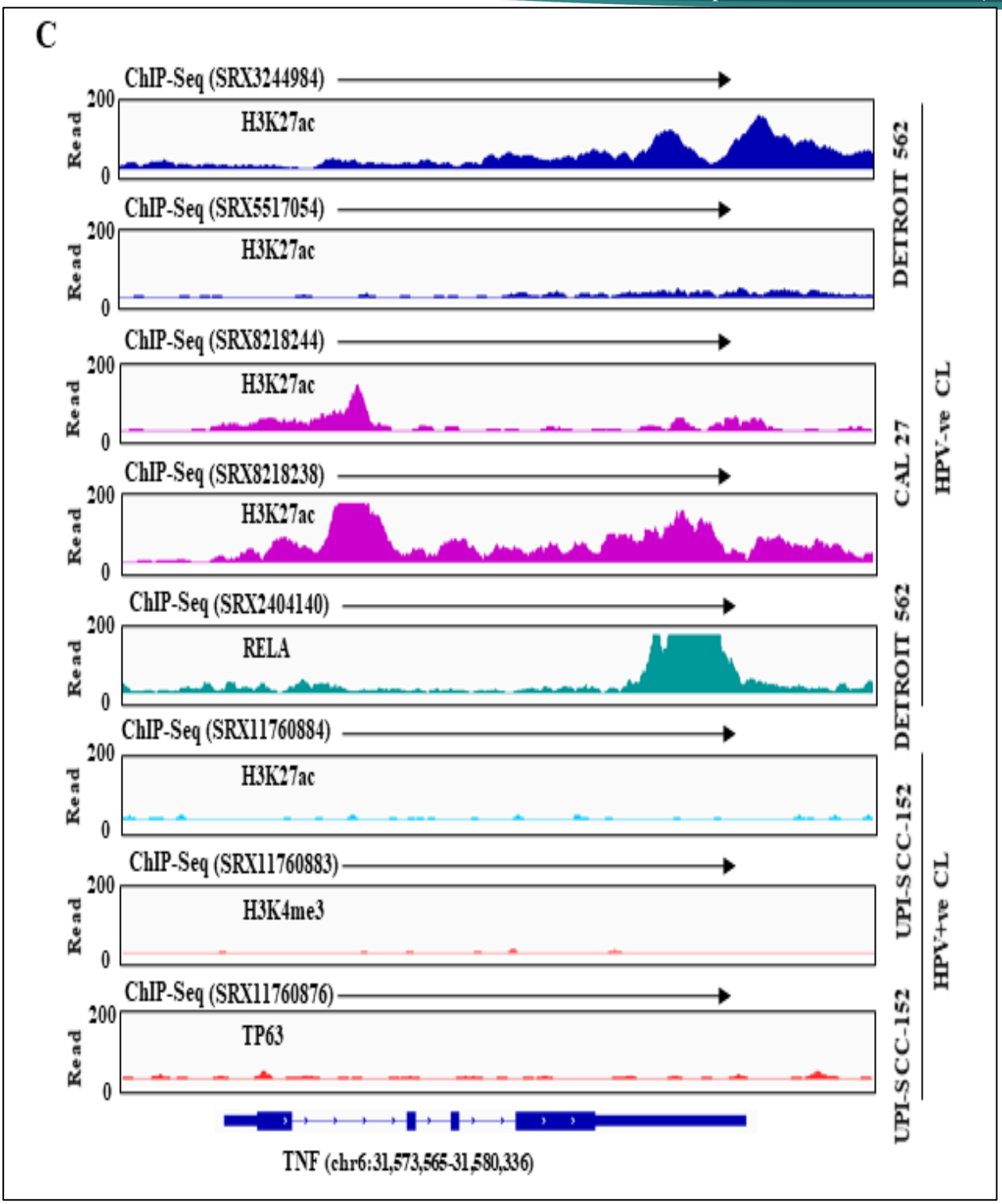

Figure 3. Chromatin and transcriptional regulation at pro-inflammatory cytokine loci in HPV-positive and HPV-negative HNSCC. (A) In HPV-negative cells, the IL1Aα promoter region shows strong enrichment of H3K27ac along with RELA binding, indicating an actively transcribed state. In contrast, HPV-positive cells lose this acetylation mark, reflecting transcriptional repression, with minimal H3K4me3 or P63 binding detected. (B) A comparison of IL1β loci reveals a similar trend, where HPV-positive cells consistently display reduced H3K27ac signals compared to HPV-negative cells, pointing to widespread suppression of pro-inflammatory gene activity. (C) When integrating transcription factor binding with chromatin accessibility, HPV-positive cells show decreased p63-associated enhancer activity, suggesting that weakened regulatory interactions contribute to reduced cytokine expression. CL – Cell Line.

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The differentially expressed genes were collected from the RNA-seq data of Figure 2C for pathway analysis. The analysis showed the top five pathways most significantly downregulated in HPV-positive tumors: Cytoskeleton in muscle cells, Human papillomavirus infection, Protein digestion and absorption, Focal adhesion, and ECM–receptor interaction. Many of these pathways are involved in cell–cell and cell–matrix communication, which are essential for immune cell recruitment and inflammatory signaling. In particular, the suppression of focal adhesion and ECM–receptor interaction points to weakened communication between the tumor and its surrounding microenvironment, which may restrict the infiltration and activation of pro-inflammatory immune cells (Khalaf et al., 2021). This reduction in structural and adhesion signaling pathways aligns with the observed decrease in pro-inflammatory cytokine expression (Figure 2B–E). The only thing that remains is to prove how these pro-inflammatory cytokines are suppressed by HPV infection. Together, the data suggest that HPV-positive tumors not only suppress cytokine production but also change the pattern of cell-cell adhesion and extracellular matrix signaling. This ultimately creates a microenvironment less capable of supporting a heightened and prolonged inflammatory response. We can also suggest that HPV-positive HNSCC tumors still progress to advanced stages (Figure 2A), but they do so within a very much different cytokine environment (Figure 2B–E). The thorough reduction in pro-inflammatory cytokines, many of which are also standard HNSCC biomarkers, offers a likely explanation for why patients with HPV-positive tumors tend to have a better prognosis (as shown in Figure 1E). In essence, HPV-mediated suppression of inflammatory signals also makes the early detection of HNSCC more difficult due to the lower expression of typical cytokine biomarkers. Interestingly, it is already known that many of the oncogenic genes, including MMP1, MMP11, PTHLH, and SPRR2G, are transcriptionally regulated by cytokine-driven NF-κB and MAPK signalling (Eiró et al., 2013; Hiremath & Wysolmerski, 2013; Vincenti & Brinckerhoff, 2002; Zabini et al., 2023). Since our data revealed broad suppression of pro-inflammatory cytokines such as IL1α, IL1β, and TNF, it is likely that this upstream repression feeds directly into the lowered expression of cancer progression and invasion-associated genes. This observation suggests that HPV-positive tumors not only dampen immune signalling but also indirectly restrain matrix degradation and metastatic potential through cytokine–oncogenic gene crosstalk.

HPV-Mediated Chromatin Remodeling at IL1α, IL1β, and TNF Promoters Suppresses Cytokine Expression by Replacing RELA with p63

Our next analysis illustrates how HPV infection reshapes chromatin regulation at key pro-inflammatory cytokine loci, explaining for their reduced expression. In Figure 3A, the HPV-negative cell line displays strong enrichment of H3K27ac at the IL1α promoter, along with a major transcription factor RELA binding, hallmarks of active transcription. In contrast, the HPV-positive cell line shows loss of this acetylation mark, with only a faint H3K4me3 signal remaining, proving a clear promoter repression. Notably, at the promoter site, p63 replaces RELA. This finding is significant. As p63 is a master regulator in HPV positive cellular systems, it modifies a total of epithelial development, stemness, and survival, which align with the epithelial environment in which HPV integrates (Martins et al., 2023). By recruiting p63 to the IL1α promoter, HPV effectively changes the cellular regulation, shifting from inflammatory signalling towards pathways that sustain epithelial persistence. This not only suppresses cytokine expression but also reinforces an epithelial program that facilitates viral maintenance and slower carcinogenesis development, citing a lower expression of oncogene and higher survival in figure 1. A similar regulatory pattern is observed in Figure 3B at the IL1β locus and in Figure 3C at the TNF locus. In HPV-negative cells, these sites exhibit RELA-driven active chromatin, marked by H3K27ac, whereas HPV-positive cells show a loss of acetylation, reduced H3K4me3, and p63 occupancy, indicating an overall lower expression profile of pro-inflammatory cytokines. Collectively, all of these results demonstrate that HPV suppresses inflammatory cytokine transcription by replacing

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RELA activity with p63 binding and it also can modulate epigenetic reprogramming which silences immune signalling while increasing epithelial identity. It explains how this whole hijacking of genes by the virus contributes to immune detection and slow but deadly cancer progression.

Discussion

Our findings highlight a central paradox in HPV-driven head and neck cancers. Although HPV-positive tumors often present at advanced clinical stages, they display suppressed oncogenic gene expression and significantly better survival outcomes compared to HPV-negative cases. This appears to be partly explained by HPV's ability to reprogram host chromatin and immune regulatory networks. The genes, MMP1, MMP11, PTHLH, and SPRR2G are key oncogenic drivers in HNSCC. MMP1 and MMP11 are matrix metalloproteinases that degrade the extracellular matrix and facilitate invasion and metastasis (Cabral-Pacheco et al., 2020); PTHLH promotes tumor growth and bone involvement (Lv et al., 2014); and SPRR2G is linked to epithelial differentiation and stress response (Patiyal & Agrawal, 2025). While these genes are highly expressed in HPV-negative HNSCC, surprisingly, we found their expression to be significantly lower in HPV-positive tumors.

Importantly, the reduced expression of *MMP1, MMP11, PTHLH,* and *SPRR2G* in HPV-positive tumors may be mechanistically linked to upstream cytokine suppression. Pro-inflammatory cytokines such as *IL1α, IL1β,* and *TNF* are well-established inducers of NF-κB/MAPK signalling cascades that drive MMP and epithelial remodelling gene expression. Thus, by repressing cytokine production through loss of H3K27ac and replacement of RELA with p63, HPV-positive HNSCC tumors simultaneously attenuate the inflammatory program and downstream oncogenic drivers of invasion. This creates a unified model in which cytokine repression and reduced oncogene activation are not separate phenomena, but rather sequential consequences of viral chromatin reprogramming. Such coupling of immune dampening with decreased invasive capacity provides a compelling explanation for the paradoxical clinical profile of HPV-positive HNSCC—advanced stage at presentation yet improved survival. So, this reduction is biologically meaningful because it suggests that HPV-positive cancers suppress not only immune signalling but also critical pathways related to invasion, metastasis, and epithelial remodelling. Their downregulation likely contributes to the less aggressive clinical behavior of HPV-positive tumors, allowing them to reach advanced stages but with diminished malignant potential. We also observed consistent suppression of pro-inflammatory cytokines in HPV-positive cases. Genes such as IL1α, IL1β, and TNF—which are strongly upregulated in HPV-negative tumors—were significantly reduced in HPV-positive ones. This finding is important because these cytokines are both central mediators of inflammation and widely used biomarkers in HNSCC diagnosis and prognosis (Denaro et al., 2022). Their reduced expression may delay detection of HPV-positive cancers, since traditional biomarker strategies often depend on inflammation-related signatures. Moreover, dampened cytokine signaling reshapes the tumor microenvironment into a less inflammatory state, altering immune cell recruitment and tumor–host interactions (Zhao et al., 2025). Interestingly, HPV-positive tumors still progress to stage III–IV at rates comparable to HPV-negative cases, yet their clinical outcomes are more favorable. This suggests that while tumor growth and anatomical spread are not impaired, biological aggressiveness and tumor-microenvironment interactions are fundamentally altered. Pathway enrichment analyses supported this, showing suppression of adhesion and extracellular matrix (ECM) pathways. Disruption of ECM–receptor interactions and focal adhesion signaling indicates weaker tumor–stromal communication and reduced recruitment of immune effector cells (Yuan et al., 2023). Together, these changes create a microenvironment less capable of sustaining chronic inflammation, a hallmark of cancer progression.

At the mechanistic level, our integration of epigenomic datasets uncovered how HPV fundamentally reshapes chromatin states at cytokine promoters. In HPV-negative cells, these regions exist in an active transcriptional state, marked by strong enrichment of H3K27ac—a well-known

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activation signal that defines powerful enhancers and promoters (Zhang et al., 2020). At the same time, RELA (the NF-κB subunit) is bound at these promoters, driving robust transcription of key pro-inflammatory cytokines such as IL1α, IL1β, and TNF. The combined presence of H3K27ac and RELA occupancy fuels a strong inflammatory program, which activates immune responses, fosters tumor-associated inflammation, and promotes aggressive clinical behavior. In contrast, HPV-positive cells display a dramatically altered chromatin landscape. The H3K27ac signal disappears, reflecting loss of enhancer activity and suppression of inflammatory gene expression. Instead, only a weak H3K4me3 signal remains at these promoters. While H3K4me3 is typically associated with transcription initiation (Wang & Helin, 2025)In this setting, its faint presence suggests a "poised" or repressed state rather than active transcription. Notably, RELA occupancy is replaced by p63, a master regulator of epithelial identity and stemness (Li et al., 2023). This substitution signals a critical transcriptional reprogramming event: instead of supporting inflammatory transcription, these promoters are redirected toward epithelial persistence and survival pathways. This dual remodeling—loss of H3K27ac and RELA alongside weak retention of H3K4me3 and gain of p63—explains how HPV-positive tumors silence pro-inflammatory cytokine expression while reinforcing epithelial programs that sustain viral persistence and tumor survival. Importantly, this mechanism highlights how HPV reshapes promoter architecture to promote immune evasion and epithelial stability over inflammation and invasion. Despite this immune dampening, HPV-positive tumors are not immunologically "invisible." They remain strongly immunogenic, as shown by their favorable responses to radiotherapy and immunotherapy (Tufail et al., 2025). This suggests that while innate inflammatory signaling is suppressed, adaptive immune recognition is preserved, potentially explaining the paradoxical clinical advantage of HPV-positive HNSCC.

In summary, HPV-positive HNSCC demonstrates how viral reprogramming of chromatin—through loss of H3K27ac, faint retention of H3K4me3, and replacement of RELA with p63—silences cytokine transcription while supporting epithelial persistence. This epigenomic switch, together with suppression of oncogenic drivers (MMP1, MMP11, PTHLH, SPRR2G), produces a distinct tumor microenvironment that allows disease progression to advanced stages yet underlies improved patient outcomes.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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